Tertiary Butanol

CAS Number 75-65-0

US EPA HPV Challenge Program
Final Submission

Overview of Robust Summaries

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Submitted by:

Propylene Carbonate / t-Butyl Alcohol HPV Committee

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I. INTRODUCTION

The Propylene Carbonate and Tertiary Butyl Alcohol HPV Committee and its member companies have committed voluntarily to develop screening level human health effects, environmental fate and effects, and physicochemical test data for tertiary butyl alcohol under the Environmental Protection Agency's High Production Volume Challenge Program. Robust Summaries and a Test Plan were submitted to EPA April 10, 2002. The Committee has now completed the proposed testing and submits this final report. All SIDS level I endpoints have reliable and adequate data.

Manufacture and Use

t-Butanol is manufactured in a closed system as part of the process of manufacture of propylene oxide. It is used primarily in the manufacture of methyl t-butyl ether, a gasoline oxygenate. During its manufacture and primary use, there is little human exposure to t-butanol. High purity t-butanol is used as a solvent. There are no known consumer markets for t-butanol.

II. DATA SUMMARY

Endpoint	Previous Data Adequate	Testing Recom-mended	Endpoint Value
Melting Point	Yes	No	25°C
Boiling Point	Yes	No	81°C
Vapor Pressure	Yes	No	31 mm Hg @ 25°C
Partition Coefficient	Yes	No	Log Pow: 0.37
Water Solubility	Yes	No	1000 g/l @ 25°C
Stability in Water	Yes	No	Stable
Transport	Yes	No	50% to water; 40% to soil
Photodegradation	Yes	No	Does not absorb UV
Biodegradation	Yes	Complete	Not readily biodegradable
Acute Toxicity to Fish	No	Complete	LC_{50} > 961 mg/l
Acute Toxicity to Invertebrates	Yes	No	EC_{50} = 5504 mg/l
Acute Toxicity to Aquatic Plants	No	Complete	$EC_{50} \geq$ 976 mg/l
Acute Tox – Oral	Yes	No	LD_{50} = 2733 mg/kg
Acute Tox – Dermal	Yes	No	$LD_{50} \geq$ 2000 mg/kg
Acute Tox – Inhalation	Yes	No	$LC_{50} \geq$ 14,100 ppm
Gene Tox *in vivo* – MN	Yes	No	Negative
Gene Tox *in vitro* – Ames	Yes	No	Negative
Repeat Dose – Oral (90 day)	Yes	No	Rat, Male: LOEL 1.25 mg/ml Rat, Female: LOEL 2.5 mg/ml Mice: NOAEL 5 mg/ml
Reproductive Toxicity	No	Complete	Parental Tox: NOAEL = 60 mg/kg/day Dev/Repro Tox: NOAEL = 400 mg/kg/day
Developmental Tox	Yes	No	Not a teratogen Maternal Tox: LOEL = 2000 ppm Dev. Tox: LOEL = 2000 ppm

A. Physical Chemical Data

The physical /chemical data for t-butanol are found in standard reference works. The underlying data were not found, but additional testing is not justified. No data on the photodegradation of t-butanol are available. Because t-butyl alcohol does not absorb light in the region of 290-800 nm, photodegradation testing is not required by guideline (see EPA 835.2310).

Testing Conducted:

Transport and Distribution between Environmental Compartments (EQC Level III modeling)

Data on the transport of t-butanol between environmental compartments has been estimated using EPIWIN; t-butanol will partition mostly to water and soil.

Biodegradation

Based on OECD method 301B, which measures CO_2 evolution, t-butanol is not readily biodegradable. Less than 5% of the theoretical CO_2 was released during the 28 days. More than 54% of the dissolved organic carbon (DOC) was removed, but this was also less than 60% (Belarde, 2003).

B. Ecotoxicity

A study of limited value on the acute toxicity of TBA to goldfish (*Carassius auratus*) was published in 1979 (Bridie et al., 1979). The study does not meet EPA or OECD study guidelines, and does not contain details of study conduct or results. Therefore, an acute toxicity study in fish was recommended **(OECD Guideline 203 or EPA Guideline 850.1075)**.

The government of Germany performed a study (Kühn et al., 1989) of the toxicity of a number of chemicals to *Daphnia*. While some study details are not reported, the study is generally sound. Therefore, no additional testing was recommended.

No studies of TBA toxicity to algae were available, an acute toxicity study in algae was recommended **(OECD Guideline 201)**.

Testing Conducted:

Acute Fish Toxicity (OECD Guideline 203)

t-Butanol did not cause toxicity or death during 96 hours of flow-through testing of fathead minnow at levels up to 961 mg/l, measured concentration (Hughes, 2003).

Algal Toxicity (OECD Guideline 201)

t-Butanol did not affect cell density, area under the growth curve, or growth rate of unicellular green alga, *Selenastrum capricornutum*, after 72 and 96 hours of exposure at levels up to 976 mg/l, measured concentration (Hughes, 2003).

C. Mammalian Toxicity

Acute Toxicity

Numerous acute toxicity tests are available on t-butyl alcohol. Oral, dermal and inhalation tests all meet OECD and EPA test guidelines. t-Butanol has low acute toxicity. The oral LD_{50} is 2733 mg/kg; the dermal LD_{50} is > 2000 mg/kg. By inhalation, the LC_{50} is >14,100 ppm from a 4 hour whole body exposure to t-butanol vapor; ataxia and dyspnea were seen immediately post exposure at 9700 or 14,100 ppm. No further testing is recommended

Repeated Dose Toxicity

NTP performed short term and chronic carcinogenesis studies in both mice and rats by administration in drinking water. In rats t-butanol caused kidney toxicity at concentrations of 1.25 to 5 mg/l and increased kidney tumors in male rats at 5 mg/l (420 mg/kg/day). In mice t-butanol caused thyroid toxicity at concentrations of 10 to 20 mg/l and marginally increased thyroid tumors in females at 20 mg/l (2110 mg/kg). No further testing was recommended.

Mutagenesis Studies

There are two Ames assays; both are negative. There are two mouse lymphoma assays; both are negative. There is an *in vitro* sister chromatid exchange assay that was positive without activation, but negative with activation. Blood taken from mice in the 90 day NTP study were analyzed for micronuclei; TBA did not induce an increase in MN. The mutagenicity battery is satisfactory; no further mutagenicity testing was recommended.

Developmental Toxicity/Teratogenicity

A developmental toxicity study is available in rats. Maternal toxicity (decreased weight gain and feed consumption at 5000 ppm; unsteady gait at 3500 and 5000 ppm and decreased locomoter activity at 2000 ppm) was seen at all exposure concentrations. Developmental delay (reduced fetal weight, reduced ossification) occurred in offspring of dams exposed during gestation to 2000 ppm or greater; however, no increase in malformations was seen. Results from two developmental toxicity studies in mice are available. Neither of the studies is compliant with either OECD or EPA guidelines for developmental toxicity testing; however, neither study demonstrated increased malformations. There is sufficient information to determine that t-butyl alcohol has limited ability to cause malformations. No further developmental toxicity testing was recommended.

Toxicity to Reproduction

No studies of the effect of t-butanol on reproductive function were available. No adverse effects were observed in sex organs in rats or mice in the subchronic or chronic studies of t-butanol conducted by NTP. However, several observations (*i.e.*, decreased fetal body weights in teratology studies, altered postnatal development) suggest that further study of reproductive toxicity is warranted. An enhanced OECD 421 study was proposed and to investigate the effect of t-butanol on mating behavior, preimplantation, embryonic and fetal development, parturition, and postnatal survival and development until weaning.

Testing Conducted:

An enhanced **OECD Guideline 421** study on t-butanol was conducted (Hazelden, 2004). t-Butanol was administered by gavage to F_0 male and female Sprague-Dawley rats for 4 weeks premating. Males were treated for a total of 9 weeks, after which sperm were analyzed for total number, abnormal morphology, and motility. Females were treated through mating, through day 20 gestation and lactation days 5-21.

In males at 1000 mg/kg/day, there was an initial reduction in body weight gain, which remained as a 5-7% deficit in weight until termination. During late gestation, there was a reduction in weight gain in females. At 1000 mg/kg/day, there was transient lethargy, and ataxia. At 400 mg/kg/day similar effects were seen in a few females during weeks 2-4. There was no effect on mating or fertility; 11-12 females in each group became pregnant and all delivered a live litter. All but three females mated at the first estrus (one each in 0, 64, and 160 mg/kg/day groups). There was a questionable increase in gestation length at 400 and 1000 mg/kg/day. All females delivered within the normal range of 21-23 days; however, 6 of 11 females at 1000 mg/kg/day and 5 of 12 at 400 mg/kg/day vs. no more than 20% in any of the control and lowest two treatment groups delivered on day 23.

There was no effect on sperm motility or sperm morphology. There was no effect on the number of implantation sites per pregnancy. At 1000 mg/kg/day, there was a significant reduction in the number of live born pups and an increase in the number of still born pups. The mean litter sizes on postnatal day 1 were: 15.2, 13.8, 13.5, 14.1 and 10.2** for 0, 64, 160, 400 and 1000 mg/kg/day, respectively; ** = $p < 0.01$. Following reduction of litter sizes to 10 pups/litter on postnatal day 4, postnatal day 21 mean litter sizes were: 10.0, 9.9, 9.3, 9.9, and 7.6**. F_1 offspring born to dams treated at 1000 mg/kg/day had lower body weight on day 1, which continued throughout gestation. At weaning, males weighed 11% less than control and females 6% less than control.

F1 pups (1 male, 1 female/litter) were treated at the dose levels as their parents for 1 week (postnatal days 21-27). There were no clinical signs of toxicity at any dose during the one week of treatment. The decreased body weight at weaning was maintained without change during the week.

The NOAEL for paternal and maternal toxicity was 160 mg/kg/day t-butanol. Maternally toxic doses of t-butanol (1000 mg/kg/day) resulted in decreased survival and body weight of pups. The NOAEL for reproduction/development was 400 mg/kg/day. Direct exposure of pups for one week after weaning did not exhibit further toxicity.